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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/148,973	09/04/98	GREENAMYRE J	PC10023A

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EXAMINER	
HSU,G	
ART UNIT	**PAPER NUMBER**
1627	10

DATE MAILED: 06/20/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/148,973	Greenamyre et al.
Examiner	**Group Art Unit**
Grace Hsu, Ph.D.	1627

☒ Responsive to communication(s) filed on *Apr 4, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-8* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-3 and 5-7* is/are rejected.

☒ Claim(s) *4-8* is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

1. The Communication in Response to September 28, 1999 Office Action received on April 4, 2000 was entered as Paper No. 8 and The Request Under 37 C.F.R. 1.19 To Correct Filing Receipt received on April 20, 2000 was entered as Paper No. 9.

2. This Office Action is in response to the March 27, 2000 Communication in Response to the September 28, 1999 Office Action.

Status of Claims

3. No claims have been allowed in the instant application.

4. Claims 1-8 are pending and under examination in the current application.

5. Claims 4 and 8 have been indicated to be allowable subject matter in the September 28, 1999 Office Action.

Claims 4 and 8 remain objected to as being dependent upon a rejected base claim and would be allowable if rewritten in independent form to include all limitations of the base and any intervening claims. Claims 4 and 8 are limited to administration of 3-(2-chlorophenyl)-2-[2-(6-diethylaminomethyl-pyridin-2-yl)-vinyl]-6-fluoro-3H-quinazolin-4-one. That compound is not taught in the prior art, but appears for the first time in the literature in one or more of Applicants' disclosures, all of which were published less than one year prior to the critical date. Thus, 3-(2-chlorophenyl)-2-[2-(6-diethylaminomethyl-pyridin-2-yl)-vinyl]-6-fluoro-3H-quinazolin-4-one was not known to be an AMPA receptor antagonist prior to the critical date.

Outstanding Rejections

6. The text of statutory sections of Title 35 of the U.S.Code not recited in the instant action are set forth in the previous September 28, 1999 Office Action.

7. Claims 1-3 and 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arnold et al. (U.S. Patent No. 5,670,516, Filed: June 1, 1995, Issued: December 29, 1987).

The claimed invention is directed to a method of treating dyskinesia, which comprises administering to a mammal an amount of an AMPA receptor antagonist that is effective in treating said dyskinesia.

Arnold et al teach a method of treating neurological disorders by administering a compound that blocks (or antagonizes) AMPA receptors. It is acknowledged that Arnold et al exemplify different AMPA antagonist compounds. However, instant claims 1-3 and 5-7 are not limited to particular AMPA antagonists.

In view of the above, Arnold et al. ***differs*** from the claimed invention in that the claimed invention is drawn to treating a more specific neurological disorder, namely dyskinesia associated with dopamine agonist therapy (claims 1 and 5), wherein the therapy comprises administration of L-dopa or L-dopa in combination with an inhibitor of peripheral dopadecarboxylase (claims 2 and 6), wherein the peripheral dopadecarboxylase is cardidopa or benserazide (claims 3 and 7).

A person of ordinary skill in the art would have been motivated to use AMPA antagonists to treat dyskinesia, in view of the patent's entire disclosure, because the Arnold et al. teach that dyskinesia is among those neurological disorders responsive to AMPA antagonists.

A person of ordinary skill in the art would have had a reasonable expectation of success to use AMPA antagonists to treat dyskinesia, in view of the patent's entire disclosure, because the Arnold et al. teach that dyskinesia is among those neurological disorders responsive to AMPA antagonists.

It would have been ***prima facie obvious*** to a person of ordinary skill in the art to use AMPA antagonists to treat dyskinesia, in view of the patent's entire disclosure, because Arnold et al teach that blocking AMPA receptors is an effective way to treat a variety of disorders, including dyskinesia (see, for example, claims 24 and 29).

8. Claims 1-3 and 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klockgether et al. (Annals of Neurology, 1991, 30, 717-723).

Klockgether et al. teach that blocking AMPA receptors (by administering AMPA receptor antagonists) may provide a new strategy for treating Parkinson's disease (PD).

In view of the above, Klockgether et al. ***differs*** from the claimed invention in that the claimed invention is drawn to treating dyskinesia associated with L-dopa therapy.

A person of ordinary skill in the art would have been motivated to develop a method for treating dyskinesia associated with L-dopa therapy, because: (1) Klockgether et al suggest treating PD patients who are on L-dopa therapy, as they suggest that AMPA antagonists can "potentiate" the actions of l-dopa, but reduce tremor associated therewith. (see, page 18, column 2); and (2) Klockgether et al suggest dyskinesia associated with l-dopa therapy, because Parkinson disease symptoms, include tremors, a main symptom that results in dyskinesia.

A person of ordinary skill in the art would have had a reasonable expectation of success to develop a method for treating dyskinesia associated with L-dopa therapy, because (1) Klockgether et al suggest treating PD patients who are on L-dopa therapy, as they suggest that AMPA antagonists can "potentiate" the actions of l-dopa, but reduce tremor associated therewith. (see, page 18, column 2); and (2) Klockgether et al suggest dyskinesia associated with l-dopa therapy, because Parkinson disease symptoms, include tremors, a main symptom that results in dyskinesia.

It would have been ***prima facie obvious*** to a person of ordinary skill in the art to modify the process implied by Klockgether et al. in light of the foregoing.

9. Claims 1-3 and 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stella et al. (Annals of Neurology, 1996, 39, 574-578) in view of Klockgether et al. (Annals of Neurology, 1991, 30, 717-723).

Stella et al. teaches administering glutamate antagonists to treat dyskinesias associated with l-dopa therapy in Parkinson's disease.

In view of the above, Stella et al. ***differs*** from the claimed invention in that the claimed invention call for administration of an AMPA receptor antagonist as the glutamate antagonist.

A person of ordinary skill in the art would have been motivated to make the aforementioned substitution because, Klockgether et al teach that both AMPA antagonists and NMDA antagonists are glutamate receptor antagonists (see, page 1, column 2).

A person of ordinary skill in the art would have had a reasonable expectation of success to make the aforementioned substitution, because Klockgether et al teach that both AMPA antagonists and NMDA antagonists are glutamate receptor antagonists (see, page 1, column 2).

It would have been ***prima facie obvious*** to a person of ordinary skill in the art to modify the teaching of Stella et al. with the teachings of Klockgether et al. to use AMPA antagonists as the glutamate receptor antagonists, rather than the NMDA receptor antagonist.

Applicants' March 27, 2000 Arguments and Examiner's Responses

10. Applicant's arguments filed in the March 27, 2000 Communication have been fully considered, but they are not persuasive.

All rejections made in the previous September 28, 1999 Office Action now *are maintained* against claims for reasons of record.

11. Applicants' ***have traversed*** the rejection of claims 1-3 and 5-7 under 35 U.S.C. 103 over Arnold et al. (U.S. Patent No. 5,670,516, Filed: June 1, 1995, Issued: December 29, 1987).

With regard to Arnold et al., applicants argue that the claimed method is not obvious from the teachings of the aforementioned reference, because:

> [a] it does not teach a method of treating dyskinesia, wherein said dyskinesia is caused by dopamine therapy; and
>
> [b] that it would not be obvious to use compounds indicated for treating dyskinesias associated with glutamate toxicity to treat dyskinesias associated with dopamine therapy;

In response, the Examiner disagrees with applicants' arguments with regard to Arnold et al for the following reasons:

[a] The Arnold reference does disclose a method of treating dyskinesia, which comprises administering to a mammal an amount of a compound that is an AMPA receptor antagonist, via the blocking AMPA receptors by administration of AMPA receptor antagonists. Moreover in their March 27, 2000 Communication, applicants acknowledge that the Arnold et al. reference teaches that the use of a neuroprotective agent, as an AMPA receptor antagonist is "useful in treating" neurological conditions ,which include tardive dyskinesia.

[b] In response to applicant's argument that it would not be obvious to use compounds indicated for treating dyskinesias associated with glutamate toxicity to treat dyskinesias associated with dopamine therapy, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Moreover, mechanisms of action as to how a particular condition, disease, etc. are not afforded patentable weight under the current U.S. law. As the claimed invention includes administering to a mammal an amount of some non-specified AMPA receptor antagonist, one of

ordinary skill in the art would maintain that regardless of the causative means by which such dyskinesia conditions result in any mammal, all mechanisms of biological action of the such AMPA receptor antagonists when used to treat dyskinesia conditions would invariably be inherent in mammals.

In light of the foregoing, the obviousness rejection of claims 1-3 and 5-7 under 35 U.S.C. 103 over Arnold et al. (U.S. Patent No. 5,670,516, Filed: June 1, 1995, Issued: December 29, 1987).

[2] Applicants' ***have traversed*** the rejection of claims 1-3 and 5-7 under 35 U.S.C. 103 over Klockgether et al. (Annals of Neurology, 1991, 30, 717-723).

With regard to Klockgether et al., applicants argue that the claimed method is not obvious from the teachings of the aforementioned reference, because

[a] the passage cited by the Examiner in the previous action indicating that "AMPA receptor antagonists reduce tremor associated with L-dopa" could not be located by applicants;

[b] it only discusses side effects that might have been observed with the AMPA drug and does not address any l-dopa side effects; and that

[c] "administering NBQX (an AMPA receptor antagonist) to a patient suffering dyskinesia from L-dopa therapy might actually be considered counterintuitive from Klockgether et al., since one might expect NBQX to exacerbate the dyskinesia side effect of l-dopa, since Klockgether et al. indicates that NBQX potentiates the effect of l-dopa (see, applicants response page 3, lines 25-28)"; and

In response, the Examiner disagrees with applicants' arguments with regard to Klockgether et al. for the following reasons:

[a] The Examiner notes that an inadvertent page number misidentification lead to confusion with regard to the specific Klockgether et al. citation (i.e., stating that treating PD patients who are on L-dopa therapy, wherein AMPA antagonists can "potentiate" the actions of l-dopa, but reduce tremor associated therewith). The passage cited by the Examiner is located on page 720, col. 2, lines 1-15 of the reference, not on page 18, column 2 of the facsimile transmission page from the Pfizer library.

[b] and [c] The Examiner disagrees with applicants' contention that Klockgether et al.: [1] only discusses side effects that might have been observed with the AMPA drug without addressing L-dopa side effects; and that [2] administration of the NBQX receptor antagonist would be expected to exacerbate the dyskinesia side effect of l-dopa.

With respect to the Klockgether reference, the Examiner maintains that applicants have mischaracterized the teachings discussed therein and notes:

> "the principal finding of [Klockgether's] research are that the selective AMPA receptor antagonist NBQX has potent anti-parkinsonian effects . . .[in] that it ***potentiates the actions of L-dopa*** (see, page 720, col. 2, lines 11-15) ***and is effective in reducing the overall activity of neuronal activity*** (see, page 717, lines 17 to page 718, lines 1-2) ***associated with Parkinson's disease***, such as dyskinesia, tremors, etc, due to clockade of excitatory synaptic transmission by AMPA receptor antagonists (see, abstract, line 12-13)."

In particular, Klockgether et al. teaches that:

[1] co-administration an AMPA receptor antagonist and L-DOPA were administered to said mammals to reduce symptoms typically associated with Parkinson's disease, including tremors and dyskinesia

(i.e. NBQX, a AMPA receptor antagonist with a selective affinity for AMPA receptors, with therapeutic effects related only to AMPA receptor blockade was administered in combination with L-dopa (i.e., in l-dopa agonist therapy; see, e.g., page 719, lines 7-11 and Fig. 1) to mammals, (see, page 718, col. 1, lines 2-4 and page 721, col. 2, lines 1-10);

[2] wherein the AMPA receptor antagonist **potentiates or makes l-dopa more effective** in the treatment of Parkinson's disease symptoms, because it reduces and/or eliminates side effects associated with the administration of either antagonist or L-dopa drug, such as dyskinesias (see, page 720, col. 1, lines 8-10);

[3] typical parkinsonian features (tremor, posture, gait, etc.) and drug related side effects (such as dyskinesias, vomiting and psychological disturbances) ***were not observed in laboratory animals*** (see, page 718, col. 2, lines 12-16) based upon the combination therapy of antagonist and L-dopa; and that

[4] selective AMPA receptor antagonists have recently been reported to prevent neurotoxicity of L-dopa in an in vitro test system and they may therefore ***prevent some long term adverse effects of L-dopa treatment*** (see, page 723, col. 1, lines 6-10).

Moreover, applicants' instant disclosure, defines the phrase "dyskinesia associated with dopamine agonist therapy" to mean ***"any dyskinesias which accompanies, or follows in the course of, dopamine agonist therapy, or which is caused by, related to, or exacerbated by dopamine agonist therapy, wherein dyskinesia and dopamine therapy are defined therein*** (see, applicants specification, page 3, lines 20-24 and page 2, lines 32-40 to page 3, line 1-19)." Applicants admission in their response further support the fact that in L-dopa agonist therapy

"NBQX (a selective AMPA antagonist) potentiates the actions of L-dopa and was not observed to produce apparent side effects (dyskinesias, vomiting or psychological disturbances) at the doses tested."

In clight of the foregoing, Klockgether discusses side effects associated from either or both AMPA receptor antagonists or L-dopa, alone or in combination (see, experimental discussion section and Fig. 1, results of administration of L-dopa, alone or with AMPA receptor antagonist); and that [2] administration of the NBQX receptor antagonist reduces the side effects of L-dopa administration, including dyskinesias.

The obviousness rejection of claims 1-3 and 5-7 under 35 U.S.C. 103 over Klockgether et al. is maintained.

[3] Applicants' have traversed the rejection of claims 1-3 and 5-7 under 35 U.S.C. 103 over Stella et al. (Annals of Neurology, 1996, 39, 574-578) in view of Klockgether et al. (Annals of Neurology, 1991, 30, 717-723).

With regard to Stella et al. in view of Klockgether et al., applicants argue that:

> [1] Stella teaches that [1] dyskinesias resulting from l-dopa treatment are limited to NMDA receptor antagonists; and that [2] any glutamate antagonist other than an NMDA antagonist can be used against dyskinesias induced by l-dopa treatment; and
>
> [2] Klockgether et al. does not compensate for this deficiency, because it was published prior to Stella et al. and merely demonstrates that AMPA receptor antagonists were available prior to the Stella et al. reference.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Although the aforementioned references were separately argued by the applicants, it is noted by the Examiner that: [a] the combined teaching of those references bolsters the obviousness to use AMPA receptor antagonist as the glutamate antagonist, because one of Klockgether et al. teaches that the antagonists used therein are a selective antagonist of the AMPA subtype of glutamate receptor and both AMPA antagonists and NMDA antagonists are glutamate receptor antagonists (see, page 717, abstract, line 4-5 and col. 2).

In light of the foregoing, the obviousness rejection of claims 1-3 and 5-7 under 35 U.S.C. 103 over Stella et al. in view of Klockgether et al. Is maintained.

Conclusion

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Grace C. Hsu, Ph.D., J.D., whose telephone number is (703) 308-7005. The Examiner may be reached during normal business hours, Monday through Friday from 8:30 am to 5:30 pm (EST). A message may be left on the Examiner's voice mail.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Jyothsna A. Vencat, Ph.D. may be reached at (703) 308-2439. The fax number assigned to Group 1627 is (703) 305-4242. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1627 receptionist whose telephone number is (703) 308-0196.

Grace C. Hsu, Ph.D., J.D.

June 19, 2000

BENNETT CELSA
PRIMARY EXAMINER